PEER REVIEW HISTORY

ARTICLE DETAILS

TITLE (PROVISIONAL)	Therapist- and parent-guided Internet-delivered behaviour therapy for paediatric Tourette's Disorder: a pilot randomised controlled trial with long-term follow-up
AUTHORS	Andrén, Per; Aspvall, Kristina; Fernández de la Cruz, Lorena; Wiktor, Paulina; Romano, Sofia; Andersson, Erik; Murphy, Tara; Isomura, Kayoko; Serlachius, Eva; Mataix-Cols, David

VERSION 1 – REVIEW

REVIEWER	Emily J. Ricketts University of California, Los Angeles, United States of America Dr. Ricketts has received research support from the National Institute of Mental Health, the Tourette Association of America (TAA), and the TLC Foundation for Body-Focused Repetitive Behaviors.
REVIEW RETURNED	08-Sep-2018

GENERAL COMMENTS	Although efforts have been made to disseminate behavioral treatment for tics, there are still a number of barriers to access. Researchers have examined internet videoconference delivery platforms for treatment delivery and are now turning towards interactive, internet treatment programs. This manuscript reports on a pilot, randomized, controlled trial of two internet-delivered, therapist- and parent-guided pediatric tic treatment programs for habit reversal training (HRT) and exposure and response prevention (ERP). The authors are careful to note that this study is not a direct comparison of HRT and ERP but is an evaluation of the degree to which the treatments can be feasibly adapted for internet delivery. Of the internet-based tic treatment programs currently being investigated (Conelea & Wellen, 2017; Jakubovski et al., 2016), the BIP TIC programs presented here appear to be unique in their use of a therapist-guided format. As the authors note, this added therapist contact seems important for improving treatment engagement and adherence. Questions and suggestions are as follows. Introduction: The authors' statement that "Therapist-guided Internet-delivered self-help programmes have proven effective for a range of different mental health problems in both children and adults, but have yet to be evaluated in TD/PTD" is correct. However, it does make sense to still mention other non-therapist-guided, internet-delivered behavioral tic treatment programs that are currently being evaluated. These include tichelper.com – an English language internet-delivered CBIT for children and families with a pre-recorded video guide-person (https://clinicaltrials.gov/ct2/show/NCT02413216; see Conelea & Wellen, 2017 for a review); and ONLINE-TICS – a

	German language internet-delivered CBIT program for adults (https://clinicaltrials.gov/ct2/show/NCT02605902; Jakubovski et al., 2016). As neither are therapist-guided, this provides a transition into describing the unique feature of the present treatment program. Conelea, C. A., & Wellen, B. C. (2017). Tic treatment goes tech: A review of tichelper.com. Cognitive and Behavioral Practice, 24, 374-381. Jakubovski, E., Reichert, C., Karch, A., Buddensiek, N., Breuer, D., & Muller-Vahl, K. (2016). The ONLINE-TICS study protocol: A randomized observer-blind clinical trial to demonstrate the efficacy and safety of internet-delivered behavioral treatment with chronic tic disorders. Frontiers in Psychiatry, 7, 119. Method: It makes sense to move the Power calculation paragraph to just before the Statistical analysis section and move the Patient involvement paragraph to just before the Intervention paragraph. I almost overlooked the patient involvement paragraph in its current location. Also I might reword it as Intervention development so it stands out. I am also interested in reading more about the development process and format of the internet delivery system. In the Patient involvement section, the authors report that five families were asked questions regarding the proposed program. So to clarify, does 'proposed program' mean they tried out a preliminary version of the internet program OR discussed a description of the programs prior to their development? The authors reported learning that patients were enthusiastic about internet-delivered interventions for tics from this discussion. Was any other information learned regarding acceptability, convenience, etc? Also, how was the treatment program finalized? The authors also report that the treatment programs include "age-appropriate texts, animations, films, and various exercises…" Can the authors expand on this description with some examples? Also, it is mentioned that eleven films were specially developed for the treatment program. Who demonstrated the tics in the videos? Was it one of the therapists or an actor? The description of the two interventions was brief. It would be helpful for the authors to add some more detail. Also, in supplementary table s1 the authors mention cognitive restructuring as one of the treatment components. I suggest adding a line in the text on this. Eligibility criteria: I suggest abbreviating "that both the child/adolescent and the parent were able to read and communicate in Swedish" to "child/adolescent and parent fluency in Swedish". The authors could also abbreviate "and that they had access to a computer connected to the Internet" to "access to a computer connected to the Internet." The authors have many measures listed so it may not be necessary to expand on all, but a bit more detail on the YGTSS scoring would be helpful since it's the primary outcome measure (e.g., "…interview with two independent ratings for tic symptom (motor and vocal) severity and tic-related impairment"), each scored on a 0-to-50 scale.

	If applicable, for the evaluator training procedure I suggest stating something to the effect of “All study assessors were trained in the YGTSS and watched xx number of video-recorded cases. Assessors achieved excellent interrater reliability (intraclass correlation = 0.98) with these cases.” Results: Did the authors track any qualitative information regarding therapist, or child and parent perspectives/satisfaction? If so, were there any themes? Also, what kinds of questions did participants ask therapists? This kind of information is always interesting to read and informative for evaluating acceptability and feasibility and modifying the intervention. Conclusion: The statement in the conclusion that “We also provide preliminary data suggesting that BIP TIC may be efficacious and cost-effective…” may need rewording, as I did not notice preliminary cost-effectiveness analysis data. I suggest removing mention of cost-effectiveness from this sentence. Without the analysis, cost-effectiveness is more of a general implication of therapist-guided, internet-delivered interventions and a future research goal. I also suggest rewording the sentence “Further evaluation of the efficacy and cost-effectiveness of this treatment modality is warranted” in the concluding sentence of the abstract for consistency. When the authors state that BIP TIC ERP might be compared to a credible control condition in a future randomized controlled comparison it may be helpful to list a few examples of credible control conditions in parentheses. For example, do the authors think a parent-guided, internet-delivered program without therapist support would be appropriate; or a parent-guided, internet-delivered program with some kind of control for therapist-attention like automated email messages and reminders?

REVIEWER	Judith Nissen Center for Children and Adolescent Psychiatry, Aarhus University Hospital, Risskov; Institute of Clinical Medicine, Health, Aarhus University Risskov, Aarhus DENMARK
REVIEW RETURNED	07-Nov-2018

GENERAL COMMENTS	This is a very interesting and very important study. It is well performed and clearly described. I only have few comments. Comment 1: Concerning the exclusion criteria, you mention acute psychiatric problems such as severe depression, suicidal risk, substance abuse or another psychiatric disorder that could interfere with treatment; a lifetime history of organic brain disorder, intellectual disability, pervasive developmental disorder, psychosis, or bipolar disorder; severe tics causing immediate risk to the patient or others and requiring urgent medical attention: Could you describe in details "other psychiatric disorders that could interfere with treatment" - which psychiatric disorders did this include? How did you evaluate intellectual disability? How did you define severe tics causing immediate risk to the patients or other - who did this evaluation, how were these patients treated, and were they included in the study following the primary treatment. Thus, there was a lower severity limit for inclusion as evaluated by YGTSS - was there an upper tic severity limit?

	Comment 2: The average number of completed chapters was 7.92 (for both children and parents; standard deviation [SD]=2.47) in the ERP group, and 7.36 (children; SD=3.04) and 7.09 (parents; SD=2.91) in the HRT group. Six children (50%) and five parents (42%) in the ERP group, and five children and parents (45%) in the HRT group completed all 10 chapters. Treatment satisfaction at post-treatment was high in both groups: A substantial number of the patients did not complete the full programme. Do you know why they chose not to complete all chapters? Did this interfere with treatment effect? and was it the same chapters, that the children/parents did not complete?

VERSION 1 – AUTHOR RESPONSE

Reviewer #1:

Introduction:

…However, it does make sense to still mention other non-therapist-guided, internet-delivered behavioral tic treatment programs that are currently being evaluated….

Reply: We thank the reviewer for this suggestion. Initially, we had left out any references to these programs since there are no published data on their efficacy, but we agree that it would give the reader a better understanding of interventions similar to ours that are emerging in the field. We have now added the following sentence (page 5), which refers to the TicHelper.com and the ONLINE-TICS programmes (in both these cases, only the study protocols have been published):

"To our knowledge, two unguided Internet-delivered programmes[11 12] are currently being evaluated in children and adults with TD/PTD (both based on HRT protocols)."

Method:

It makes sense to move the Power calculation paragraph to just before the Statistical analysis section and move the Patient involvement paragraph to just

before the Intervention paragraph. I almost overlooked the patient involvement paragraph in its current location. Also I might reword it as Intervention development so it stands out.

Reply: We have now moved the Power calculation and Patient involvement paragraphs according to the reviewer's suggestions. We have however not renamed the Patient involvement paragraph, since the BMJ Open author guidelines recommend the inclusion of a section with this title.

I am also interested in reading more about the development process and format of the internet delivery system. In the Patient involvement section, the authors report that five families were asked questions regarding the proposed program. So to clarify, does 'proposed program' mean they tried out a preliminary version of the internet program OR discussed a description of the programs prior to their development? The authors reported learning that patients were enthusiastic about internet-delivered interventions for tics from this discussion.
Was any other information learned regarding acceptability, convenience, etc? Also, how was the treatment program finalized?

Reply: The focus group was convened prior to the development of the BIP TIC program with the aim to gather views on perceived acceptability, convenience, ease of use, and efficacy. The participants were shown how the generic Internet treatment delivery platform works (this platform has previously been used in trials for numerous mental health conditions). They were also shown some mock-up pictures of proposed treatment content and features (such as the ERP stopwatch), and were described how this platform could be used in the treatment of TD/PTD. Since the BIP TIC treatments had not yet been developed, the focus group was not involved in any preliminary testing. We have now added a sentence (page 7) to make this clearer:

"Prior to the development of the BIP TIC interventions, a focus group was convened at our clinic in Stockholm, including five children with TD (and their parents). Families were asked a series of questions regarding the acceptability, convenience, ease of use, and perceived efficacy of the proposed Internet-delivered approach. In sum, we learnt that young people and their parents were enthusiastic about digital interventions for tics. ***The group was however not directly involved in the development of the treatment content.****"*

The authors also report that the treatment programs include "age-appropriate texts, animations, films, and various exercises…" Can the authors expand on this description with some examples?

Reply: Thank you very much for these comments. It is difficult to describe a graphic and interactive treatment using plain text, while still keeping it within reasonable word limits. Therefore, we refer to *Supplementary figure S1*, which includes several screenshots from both BIP TIC ERP and BIP TIC HRT. Please also see *Supplementary table S1*, which describes the content of each treatment module.

The description of the two interventions was brief. It would be helpful for the authors to add some more detail.

Reply: The description of the treatments was indeed brief but this was deliberate. Our treatments are largely based on previously published protocols/treatment manuals (see references in the manuscript). Therefore, we have just described HRT and ERP in general, and refer the reader to the above-mentioned protocols. The adaptations that were made due to the Internet treatment format are summarised in *Supplementary figure S1* and *Supplementary table S1*.

Also, it is mentioned that eleven films were specially developed for the treatment program. Who demonstrated the tics in the videos? Was it one of the therapists or an actor?

Reply: Thank you for pointing out that this was unclear. The films feature a clinical psychologist (the first author) showing different competing responses corresponding to specific muscle groups. We have now clarified this in the text (page 7):

"Eleven specifically created films, featuring a clinical psychologist (the first author), are used to illustrate a wide range of competing responses corresponding to specific muscle groups."

Also, in supplementary table s1 the authors mention cognitive restructuring as one of the treatment components. I suggest adding a line in the text on this.

Reply: Thank you for raising this point. Following this comment, we realised that the title of this module was somewhat misleading. The module does include some cognitive components, primarily how the participants can learn to identify and alter negative thoughts about their tics, but it is probably not correct to describe it as pure cognitive restructuring. The original Swedish title of the module is "Thoughts", and we have now renamed it in *Supplementary table S1* as "Negative thoughts about tics". This module is not considered a

major component in the treatments, and our experience was that the youngest participants had a hard time working with it. In fact, following our experience in the present pilot study, we have removed this module from our new version of the treatment, which we plan to evaluate in a full-scale RCT.

Eligibility criteria: I suggest abbreviating "that both the child/adolescent and the parent were able to read and communicate in Swedish" to "child/adolescent and parent fluency in Swedish". The authors could also abbreviate "and that they had access to a computer connected to the Internet" to "access to a computer connected to the Internet."

Reply: Thank you for these suggestions. We have updated the manuscript accordingly.

The authors have many measures listed so it may not be necessary to expand on all, but a bit more detail on the YGTSS scoring would be helpful since it's the primary outcome measure (e.g., "…interview with two independent ratings for tic symptom (motor and vocal) severity and tic-related impairment"), each scored on a 0-to-50 scale.

Reply: Thank you for this comment. We agree that the description was a bit scarce. We have updated the text according to your suggestion (page 9):

"The primary outcome measure was the Total Tic Severity Score of the YGTSS, a semi-structured clinician-administered interview with two independent ratings of tic symptom (motor and vocal) severity and tic-related impairment, each scored on a 0 to 50 scale."

If applicable, for the evaluator training procedure I suggest stating something to the effect of "All study assessors were trained in the YGTSS and watched xx number of video-recorded cases. Assessors achieved excellent interrater reliability (intraclass correlation = 0.98) with these cases."

Reply: We have now updated this according to the suggestion above. See below (and page 9):

"All study assessors were trained in the YGTSS and watched at total of five videorecorded cases. Assessors achieved excellent inter-rater reliability (intraclass correlation = 0.98)." **Results:**

Did the authors track any qualitative information regarding therapist, or child and parent perspectives/satisfaction? If so, were there any themes? Also, what kinds of questions did participants ask therapists? This kind of information is always interesting to read and informative for evaluating acceptability and feasibility and modifying the intervention.

Reply: Data on treatment satisfaction are shown in *Supplementary table S3*. We did not collect structured qualitative information. However, some "themes" emerged from the regular therapist communication with parents. The main feedback we received was that some of the modules were too long and had too much text.While preparing for our upcoming full-scale RCT, we have now streamlined the interventions directly in response to user feedback.

Conclusion:

The statement in the conclusion that "We also provide preliminary data suggesting that BIP TIC may be efficacious and cost-effective…" may need rewording, as I did not notice preliminary cost-effectiveness analysis data. I suggest removing mention of cost-effectiveness from this sentence. Without the analysis, cost-effectiveness is more of a general implication of therapist-guided, internet-delivered interventions and a future research goal.

Reply: Thank you for the opportunity to clarify this point. We do report that therapist support time was about 25 minutes per patient and week. As the reviewer knows, this represents a substantial time saving compared to regular face-to-face behaviour therapy for tics. We recorded this data carefully with the explicit aim to provide some proxy data for cost-effectiveness. Therefore, it is not unreasonable to hypothesise that this approach will be cost-effective.

I also suggest rewording the sentence "Further evaluation of the efficacy and cost-effectiveness of this treatment modality is warranted" in the concluding sentence of the abstract for consistency.

Reply: Please see response to the previous point. This is a central question that we will formally address in our full scale RCT.

When the authors state that BIP TIC ERP might be compared to a credible control condition in a future randomized controlled comparison it may be helpful to list a few examples of credible control conditions in parentheses. For example, do the authors think a parent-guided, internet-delivered program without therapist support would be appropriate; or a parent-guided, internetdelivered program with some kind of control for therapist-attention like automated email messages and reminders?

Reply: We have now added an example of a credible control condition (page 22):

"The results of this pilot study will inform the design of a definitive RCT to evaluate the efficacy and cost-effectiveness of BIP TIC ERP, compared to either a credible control condition (e.g., a therapist-guided Internet-delivered version of the supportive psychotherapy and education used by Piacentini et al.[2]) or other treatment modalities."

Reviewer #2:

Comment 1:

Could you describe in details "other psychiatric disorders that could interfere with treatment" - which psychiatric disorders did this include?

Reply: Thank you for the opportunity to clarify this point. We wanted to ensure that other psychiatric disorders not explicitly listed in our exclusion criteria could still be excluded if we felt that they could interfere with treatment. Examples might have included severe anxiety disorders (e.g. patients unable to travel to the clinic for assessments) or severely underweight eating disorders. However, we did not exclude any participants due to these psychiatric comorbidities. As shown in *Figure 1*, the only reasons for exclusion were: *no TD/CTD (n=7); autism (n=4); unstable medication (n=3); <7 years of age (n=2); below YGTSS threshold (n=1); previous BT for tics (n=1); organic brain disorder (n=1).*

How did you evaluate intellectual disability?

Reply: We did not formally evaluate intellectual disability. Instead, we determined whether the child went to a regular school and followed the ordinary curriculum, as a proxy for normal intellectual function. This information was gathered from the parent. We have now added this info to the manuscript (page 6).

How did you define severe tics causing immediate risk to the patients or other who did this evaluation, how were these patients treated, and were they included in the study following the primary treatment. Thus, there was a lower severity limit for inclusion as evaluated by YGTSS - was there an upper tic severity limit?

Reply: This was evaluated by the assessor (a clinical psychologist with expert knowledge in TD/PTD). There was also a senior psychiatrist in the team, which could have been consulted

if needed. The main focus was to evaluate if the tics caused any risk of physical injury that might be in need of immediate medical attention. We have added an example of risky tics to clarify this point (page 6). No participants were excluded for this reason but, had there been, the participant would have been referred to other medical services to receive medical attention, with the possibility to have been re-assessed and included in the trial later on. There was no upper tic severity limit on the YGTSS.

Comment 2:

The average number of completed chapters was 7.92 (for both children and parents; standard deviation [SD]=2.47) in the ERP group, and 7.36 (children; SD=3.04) and 7.09 (parents; SD=2.91) in the HRT group. Six children (50%) and five parents (42%) in the ERP group, and five children and parents (45%) in the HRT group completed all 10 chapters. Treatment satisfaction at post-treatment was high in both groups: A substantial number of the patients did not complete the full programme. Do you know why they chose not to complete all chapters? Did this interfere with treatment effect? and was it the same chapters, that the children/parents did not complete?

Reply: Thank you for this comment. Typically, children and parents generally completed the same number of chapters as they generally worked in parallel. There could be multiple reasons for why participants do not finish all chapters. The exact reasons were not collected systematically in our study. However, it is not unusual for participants in Internet-delivered interventions to not complete all modules. There is a clear pattern emerging in the literature that number of completed modules in internetdelivered interventions does not necessarily correlate with clinical efficacy. For example, in a previous RCT of therapist-guided Internet-delivered obsessivecompulsive disorder, conducted by our team a few years ago (Lenhard et al. 2017 *Journal of the American Academy of Child & Adolescent Psychiatry*), only 27% of participants completed all 12 treatment chapters included in the programme. Interestingly, the study showed that the number of completed chapters was not significantly correlated with the severity scores at baseline or at post-intervention. In our experience, once participants have learnt the main ingredients of the treatment (by module 4), many families prefer to continue with the treatment on their own, without necessarily logging into the BIP platform. This may give the false impression of treatment discontinuation.

VERSION 2 – REVIEW

REVIEWER	Emily J. Ricketts, PhD University of California, Los Angeles
REVIEW RETURNED	08-Dec-2018

GENERAL COMMENTS	The authors have thoroughly addressed all reviewer comments or clarified their original text. I am satisfied with their edits.

REVIEWER	Judith Nissen Children and Adolescent Psychiatric Center, Aarhus University Hospital, Aarhus
REVIEW RETURNED	04-Dec-2018

GENERAL COMMENTS	Thank you for your revised manuscript. A very interesting and well-performed study